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Anticipating Technological Change: Combinatorial Chemistry and the Environment

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Preface

The purpose of this paper is to speculate, or suggest, how combinatorial chemistry may influence the environment and environmental policy. Technological change is frequently identified as a primary determinant of how human activities affect the environment and human health. Yet policy makers often have little opportunity to posit how technology development may change or affect current policies in the future. This paper is an attempt to look at one technology, combinatorial chemistry, and to suggest how it may or may not affect our current system.

The genesis for this paper was a talk given by Dr. Paul Anderson, Vice President of Chemical and Physical Sciences, DuPont-Merck at a RAND Critical Technologies Seminar (The Critical Technologies Institute at RAND has since been renamed the Science and Technology Policy Institute). In his presentation he suggested that combinatorial chemistry would enable the simultaneous synthesis of significantly greater numbers of compounds than are routinely synthesized today. Our client, David Rejeski, then asked the questions

- Given this new capability, would our current regulatory system be able to handle a new volume of chemicals submitted for review?
- Were there other environmental effects, both positive and negative, created by this new chemical synthesis capability?

In order to respond to these questions we began with a brief review of the literature followed by interviews of experts working in industry, academia, and government. We hope this paper is useful to environmental policy makers and technologists. This work was sponsored by the Environmental Protection Agency grant program and was performed in RAND's Science and Technology Division.

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Glossary

Symbol	Definition
CPSC	Consumer Product Safety Commission
DOT	Department of Transportation
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
HPV	High Production Volume
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute of Occupational Safety and Health
OECD	Organization for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration
QSAR	Quantitative Structure Activity Relationship
QSPR	Quantitative Structure Property Relationship
SIDS	Screening Information Data Set
TRI	Toxic Release Inventory
TSCA	Toxic Substances Control Act

Introduction

In the mid-1850s, a young English lab assistant, William Henry Perkin, accidentally spilled a concoction of chemicals at his parents' home and stumbled over a purple dye while attempting to synthesize a synthetic form of quinine. To Perkin's amazement, the new dye refused to fade or run when subjected to washing or exposure to the sun. Perkin's discovery laid the groundwork for the synthetic dyestuffs industry as well as the pharmaceuticals industry (Fenichell, 1996). Then there is Adolph Spitteler's famous cat. As the story goes, the cat supposedly knocked over a bottle of formaldehyde into her saucer of milk transforming the milk into a hard substance resembling celluloid. Bingo! An early plastic was discovered (Fenichell, 1996). The history of chemical synthesis is replete with stories of both luck and perseverance.

The First World War changed this early phase of trial-and-error chemistry. Suddenly, countries realized they could be cut off from strategic resources critical to their war-fighting capabilities and the race was on to find synthetic substitutes. Building on the emerging science of polymer chemistry, new industries were developed to supply plastics, explosives, fertilizers, and dyes. As a result, by the late 1930s, chemists at the German firm I. G. Farben were busy synthesizing an average of one new compound per day (Fenichell, 1996).

Though there was an emerging science behind chemical synthesis, the discovery of new substances still depended heavily on creating, testing, and refining new combinations of chemicals. Despite significant research outlays and a team of some of the best chemists in the world, it took DuPont over a decade to perfect a silk substitute that they would later dub "nylon." At this pace, the discovery of new substances was arduous at best.

To better understand this challenge, one only has to examine the numbers. Using just six common elements, carbon, nitrogen, phosphorus, oxygen, hydrogen, and sulfur, it is possible to put together 10^{62} possible compounds with 30 or fewer atoms[1]; an impressively greater number than the $3x10^7$ compounds described in the most recent compendium *Chemical Abstracts*, which includes all of the

[1] Note, the authors could not verify this calculation and attempts to reach Dr. Anderson were unsuccessful.

compounds synthesized to date (Anderson, 1998; Chemical Abstracts Service, 2001).

Combinatorial chemistry techniques, largely applied to organic reactions for drug discovery, have redefined the speed at which chemists can synthesize new compounds. As a result of advancements in combinatorial chemistry techniques, medicinal chemists previously synthesizing 50 to 100 compounds per year, may now be anticipated to synthesize over one to two orders of magnitude more compounds per year by using combinatorial chemistry techniques.[2] This example provides a hint as to how combinatorial chemistry may alter the synthesis process typically used to discover other substances such as new materials and catalysts (i.e., heterogeneous catalysts, phosphors, thermoelectric materials, polymers). These techniques have been used for select cases of inorganic reactions for just over five years (Dagani, 1999).

Because inorganic synthesis involves heavy metals, solvents, and often requires high temperature or pressure, changes in inorganic synthesis methods have a much greater potential to affect the environment (discussed later). While combinatorial chemistry has only been used for new materials discovery and inorganic synthesis in limited circumstances, one company's experience exemplifies the potential magnitude of change. Instead of synthesizing one compound at a time, somewhere between 100 and 25,000 compounds can be synthesized simultaneously, depending on the reagents used and the goal of the specific synthesis (Symyx, 1999). Transferring these techniques to inorganic synthesis and new materials development however is non-trivial and later we will discuss some of many challenges that remain.

Perseverance is now potentially aided by a powerful and sophisticated set of capabilities. This paper explores how the expanded use and maturation of combinatorial chemistry methods may affect environmental issues and policy. Technological change is a major determinant of how human activities affect the environment and human health. The Ehrlich equation, which relates the impact any human group makes on the environment to the product of three factors—population, consumption rate (often described with GDP), and technology—is frequently used to identify the importance of technology (Ehrlich and Ehrlich, 1990). Yet policy makers often have little opportunity to postulate how technology development may change or affect current policies in the future. This

[2] Borman suggests that these chemists could be expected to synthesize somewhere between 1,000 to 40,000 compounds per year with combinatorial techniques (Borman, 1998). Another citation stated that good medicinal chemists can synthesize between 100 and 300 compounds per year using traditional synthesis methods but no comparative rates using combinatorial techniques were provided (Kuhlmann, 1997).

paper is an attempt to look at one technology, combinatorial chemistry, and to speculate how it may or may not affect our current system.

Chemicals in Commerce and the Regulatory Process

Chemicals are used to produce almost everything we consume from the food we eat to the cars we drive. Yet there are many concerns about chemicals in our environment, including but not limited to their proliferation, their persistence, and their health effects.[3] While definitive numbers do not exist, estimates are that on the order of 100,000 chemicals are used in commerce worldwide and 75,000 are registered in the United States. Worldwide more than one new chemical (including industrial chemicals, pesticides, pharmaceuticals, and food additives) is introduced every day that requires a basic set of tests of potential risk to human health and the environment according to Organization for Economic Cooperation and Development (OECD) guidelines (OECD, 1998).[4] Yet for a preponderance of chemicals in use today, we know little about carcinogenicity or other health effects.

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[3] For example, as of 1984, 10 percent of the pesticides in common use in the United States had been assessed for hazards, while for 38 percent virtually nothing was known (NRC, 1984 in Steingraber, 1997). And as of 1997 between 1.5 and 3.0 percent of the approximately 75,000 industrial chemicals in US commerce have been tested for carcinogenicity (Steingraber, 1997). Moreover, select analyses suggest that we know little about even those industrial chemicals produced in high volumes. An Environmental Defense Fund (EDF) study found that for 71 percent of high-production volume-regulated chemicals, there are insufficient data to perform a complete health hazard screening using OECD standards known as Screening Information Data Set (SIDS). This was based on a random sample of 486 high-production volume chemicals—those exceeding annual import or production of 1 million pounds. In 1990, there were 2,971 compounds listed by the EPA. EDF used for its sample those chemicals of the 2,971 that were also regulated under the Clean Water Act, Clean Air Act Amendments, Comprehensive Environmental Response, Compensation, and Liability Act, Emergency Planning and Community Right to Know Act, FIFRA, Occupational Safety and Health Act, and Safe Drinking Water Act yielding 486 chemicals. The authors randomly selected 100 of these chemicals for detailed analysis (EDF, 1997). An EPA-sponsored report found that 55 percent of the Toxic Release Inventory chemicals (numbering about 650) had full SIDS testing as compared to other chemicals, where only 7 percent had full SIDS test data. Another data set of chemicals used by children and families (numbering about 491) had full SIDS test data for only 25 percent (EPA, 1998).

[4] Minimum health hazard screening criteria, Screening Information Data Set (SIDS), were established by the OECD in 1990 and include toxicological data on: acute toxicity, repeated dose toxicity, genetic toxicity, reproductive toxicity, and developmental toxicity. Estimates of the cost to perform the basic tests for human health and the environment recommended by the OECD (called the Screening Information Data Set (SIDS)) range from $205,000 to $275,000 per chemical (EPA, 1998 and CMA, 2001).

In the United States, chemical substances are regulated by over a dozen federal statutes implemented by six different federal agencies.[5] The statutes cover a broad spectrum of activities from new chemical substance registration and testing to worker safety, to accidental releases, to food consumption; use different hazard classification systems; and cover different phases in the chemical lifecycle. Therefore, generalizations regarding the regulatory process are impossible to make.

New chemical substances are reviewed largely under three of these statutes— Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Federal Food, Drug, and Cosmetic Act (FFDCA), and Toxic Substances Control Act (TSCA), — depending on their intended use.

FIFRA covers the regulation of pesticides, defined as "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and any nitrogen stabilizer" and includes those substances produced through biotechnology, chemical, biochemical, and microbial means (Andersen and Milewski, 1999). Under FIFRA, the EPA registers pesticide products based on an assessment of potential impacts to the environment or human health. There are specific minimum testing requirements for these substances to determine health effects (short-term toxicity, carcinogenicity, reproductive toxicity, etc.), environmental effects (effects on wildlife, fish, plants, non-target organisms; contamination of groundwater or surface water) and residue safety. As of August 1998 there were over 20,000 pesticide products registered that used 860 active ingredients. Approximately 700 of these were biopesticide products (microbial, plant, and biochemical pesticides) derived from 175 distinct ingredients that were registered (EPA, 1999).

FFDCA establishes tolerances for pesticide residue on food and animal feed products. The EPA is responsible for establishing the tolerances for food and animal feed products while the FDA, USDA (meat and poultry), and the states are responsible for enforcing these limits (Steingraber, 1997). The Food Quality Protection Act of 1996 establishes tougher standards for pesticide use on food and requires the EPA to consider overall exposures to pesticides through food, water, and home environments.

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[5] These agencies are the Environmental Protection Agency (EPA), Department of Agriculture, Food and Drug Administration, Occupational Safety and Health Administration (OSHA), Consumer Product Safety Commission (CPSC), National Institute for Occupational Safety and Health (NIOSH), Food and Drug Administration (FDA), and Department of Transportation (DOT) as well as state and local governments.

TSCA defines a chemical substance as any organic or inorganic substance of a particular molecular identity, and excludes certain products that are generally regulated by other laws.[6] Testing of new chemicals can be required under TSCA *if* the EPA determines that activities associated with the chemical substance may present an unreasonable risk to human health or the environment, quantities of the substance will be large enough to generate significant exposure to humans or the environment, or there is insufficient information to evaluate the potential effects of the substance and testing is the only means to gather such information. Manufacturers are required to perform certain health tests, use quality control in their production processes, and notify the EPA of any subsequent health effects, should they occur.

Limitations of TSCA, which contribute in part to the lack of information on chemicals in commerce, are well documented.[7] For example,

> EPA's new chemical review process has enabled the agency to review over 20,000 substances in a timely manner. However the reviews do not ensure that the potential human health and environmental risks of new chemicals are fully identified because EPA has limited data on their toxic effects and exposures. TSCA does not require industry to test new chemicals for their toxicity, and industry generally does not voluntarily perform this testing (GAO, 1994).

Due to the specific language in TSCA the EPA must rely heavily on manufacturers for data and in a practical sense it has limited ability to seek additional test data. As a result, much of the EPA's analysis is based on the use of structure activity relationships (SAR) rather than direct toxicity test data (EDF, 1997; GAO, 1994).

There are indications that pressure is mounting for additional health effects and environmental fate data on both legacy and newly developed chemicals. Criticism has been voiced over the voluntary initiative established by the OECD in 1987 to increase SIDS data for being too slow—only a few hundred of the nearly 3,000 high-production volume chemicals have been tested under this program. The Toxic Release Inventory (TRI) has increased public awareness of specific chemical emissions into the environment. The Chemical Manufacturers Association, Environmental Defense and the Environmental Protection Agency

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[6] The excluded products include pesticides, tobacco products, nuclear materials, firearms, food, drugs, cosmetics, and medical devices.

[7] For example see *Toxic Ignorance: The Continuing Absence of Basic Health Testing for Top-Selling Chemicals in the United States*, Environmental Defense Fund, New York, July 1997 or *Toxic Substances Control Act: Legislative Changes Could Make the Act More Effective*, General Accounting Office, September 1994, GAO/RCED-94-103.

are collaborating to voluntarily perform additional testing for high-production volume chemicals, known as the High Production Volume Chemical (HPV) Challenge. And, the chemical industry is also working in collaboration with academic and government researchers and the EPA to develop reliable and validated screening and testing methods to help identify chemicals in the environment that have the potential to disrupt endocrine systems. If combinatorial chemistry and other novel approaches to new compound discovery have the potential to speed the discovery process, will there be fundamental changes in the ways we characterize and test new compounds? Could these techniques dramatically increase the throughput required of regulatory processes? What does this mean for new chemical synthesis in general, the environment, and for environmental policy?

Combinatorial Chemistry Techniques Will Speed the Discovery Process

Combinatorial chemistry is a technique for rapidly synthesizing new chemical compounds and materials (see Box 1 for a description). By allowing researchers to create large numbers of compounds quickly, combinatorial chemistry has been used to speed the Edisonian (trial and error) process as well as to increase the number of compounds initially explored, providing a new tool for rational design. The number of possible combinations of three or four or more elements is large. If scientists were left to synthesize one combination at a time, the universe of possibilities would not be explored for a very long time. Combinatorial chemistry addresses that problem by giving scientists the tools to synthesize a large array of compounds simultaneously or near simultaneously using a starting set of elements or reagents. These practices can potentially reduce the time-to-market and increase the likelihood of a technological breakthrough.

Some characterize it as a "dumb" technique, or a brute force method because these techniques do not necessarily require an understanding of the specific synthesis processes required for a more-targeted approach to creating new compounds. And indeed, many have found that employing combinatorial chemistry techniques just to generate large numbers of compounds is not the most effective approach—iteration to refine the synthesis process is routinely employed. Libraries created through combinatorial chemistry have also been used to improve the heuristics (generalized tools or approaches that employ empirical rules of thumb) used for catalyst or other materials development. In addition, a lot of activity is focused on employing combinatorial chemistry with algorithm development, molecular modeling, and statistical analyses to develop more precisely designed libraries.

BOX 1: COMBINATORIAL CHEMISTRY

First applied in the late 1980s, combinatorial chemistry is an approach to creating new chemical compounds by systematically combining a starting set of molecules. These starter molecules, or building blocks, are assembled in a short period of time to create a chemical library. A chemical library is a collection of compounds with varied structures that have some relationship. For example, these compounds could be related because either they have been synthesized from a given set of reagents or derived from the same plants.

There are four primary steps to creating new compounds through combinatorial chemistry—selecting the building blocks; creating the libraries; testing the library for desired properties; and isolating and identifying the new compound. Each step can be performed any number of ways. Techniques exist to create compounds in solution, linked to solid particles, or arrayed on the surface of microorganisms. Two methods to create libraries are currently employed. Split synthesis creates a series of chemical compounds by combining the building blocks in succession, separating the resultant compounds and then adding another building block, separating and adding, etc. This method requires solid support—one bead holds one compound—and as such the identification step is easier to perform. Generally this method yields small quantities of a relatively large number of compounds. Assays must be performed on groups of the resultant compounds. The other method used to create new compounds is parallel synthesis. Parallel synthesis creates compounds in separate containers and can be performed on a solid support or in solution. The use of automation simplifies this process, which produces relatively larger quantities of a smaller number of compounds. Because of the large number of compounds synthesized in parallel, it is desirable to generate small amounts of any given compound.

Selecting the reagents and planning the chemical library is the most time-intensive part of the process, while the synthesis of new compounds is relatively fast. (Testing the library for desired properties can take a long time, too.)

As with any other synthesis method, combinatorial chemistry can be used more efficiently if the link between the chemical structure and the desired activity or property is understood. The quantitative structure activity relationship (QSAR) refers to the strength of the link between the chemical structure and the specific activity desired (i.e., bioactivity). The tighter the relationship, the greater the desired activity is of the compound. Creating or identifying tight structure activity relationships is the key to optimizing chemical structures for the purposes desired. Correspondingly, quantitative structure property relationship (QSPR) is used primarily to refer to advanced materials discovery (e.g., catalytic function). Combinatorial chemistry can be used, of course, to explore new effects where little is known about the QSAR or QSPR.

Combinatorial chemistry has been applied primarily by the pharmaceutical industry where the first drugs to have been discovered using these techniques entered clinical trials in the early- to mid-1990s. New drug development is a lengthy and labor-intensive process. It takes somewhere between 9 and 13 years from the first synthesis to market acceptance (which includes drug discovery and development and clinical trials) for most drugs. Combinatorial chemistry can reduce the front-end, or the discovery phase, of this process where typically between 50,000 and 100,000 compounds are tested to identify a promising drug candidate (which must then be optimized) by an estimated 1.5 to 2 years

(Kuhlmann, 1997; Michels et al., 1998). Good medicinal chemists can synthesize between 50 and 300 compounds per year using traditional synthesis methods. Experience with combinatorial chemistry to date suggests that these numbers could rise to between 1,000 and 40,000 compounds per year on average (Kuhlman, 1997; Borman, 1998)[8]. In one combinatorial chemistry experiment alone, 57,500 compounds were synthesized in a week (with a month's preparation time) (Anderson, 1998).

Experience applying combinatorial chemistry to synthesis outside of the pharmaceutical industry for both organics and inorganics is much less developed. Needless to say data on likely synthesis rates, etc., are sparse. One company actively applying combinatorial chemistry techniques to inorganic synthesis can synthesize somewhere between 100 and 25,000 compounds in a single library depending on the chemistry used (Symyx, 1999). Information on how these numbers may translate to typical annual synthesis rates was not located.

During new product development companies typically search pre-existing or newly created libraries for compounds with desirable properties for a given application. Therefore, companies that have large libraries of compounds to search for candidate compounds, or those that have the ability to rapidly synthesize new compounds can attain a market advantage. Because of automated parallel synthesis, combinatorial chemistry techniques can reduce the time and expense it takes to synthesize new compounds and create large libraries of potentially promising compounds and, as such, provide an opportunity to explore a much greater variety of compounds.

As mentioned previously, with respect to environmental considerations, the application of combinatorial chemistry techniques to inorganic synthesis and materials science in general may provide a benefit to the environment for several reasons including a reduction in the use of undesirable materials (such as heavy metals and solvents), an improved capability to develop materials with desirable properties (such as improved thermoelectric properties), and a reduction in pollution generation because of process efficiencies. However, the extension or application of combinatorial methods to materials science can be challenging because of the need to develop new methods for high-throughput screening and synthesis, often within tight cost constraints. The next section highlights some of

[8] The Kuhlman citation gave the range of 100 to 300 compounds per year for good medicinal chemists using traditional synthesis techniques while Borman gave comparative statistics of 50 to 100 compounds per year for traditional methods and 1,000 to 4,000 compounds per year for combinatorial methods.

the areas where combinatorial chemistry may influence the environment and environmental policy. Later we will discuss some of the technological challenges that remain.

The Environment and Combinatorial Chemistry

Affects on the Regulatory Process

The first question we sought to illuminate during our research was whether or not the regulatory process would be overrun with new submissions for chemical review. The short answer is no. While many more compounds can be analyzed during the discovery process, combinatorial chemistry is not expected to dramatically increase the number of chemicals entered in commerce, primarily because of scale issues. The consensus from our interviews is that combinatorial chemistry will be used to produce better, more refined products—not more. This is largely because combinatorial chemistry is currently most effective in providing initial candidates for new materials or drug discovery. These candidates must be screened for a myriad of features desired for a commercially viable product. Thus, combinatorial chemistry will be useful to introduce and screen a greater number of candidates before large sums of money are committed for scale up and commercialization. According to an industry source, for every 20,000 potential pesticide products identified in the discovery phase, only one makes it to end-use on the farm (American Chemical Council, 2001). Even when they are in the final stages of development, many developed chemicals do not get manufactured. EPA TSCA data show that less than half (43 percent) of the new chemicals registered with a premanufacturing notice were ever submitted for a notice of commencement for 1979–1996 (note, the year-to-year percentage can vary significantly) (Seidenstein, 1999).

Counterbalancing these arguments is the notion that combinatorial chemistry could make the process of producing "designer" chemicals on demand easier—those chemicals that are modified for a specific customer's purposes. If demand for niche-chemicals proliferates, this could strain the regulatory approval process. However, at first blush it appears that combinatorial chemistry will not overwhelm the regulatory process.

In fact, combinatorial chemistry may be used to *improve* toxicity testing in the regulatory process by making it cheaper and more feasible to perform a variety of toxicity tests. Widespread application of combinatorial techniques has and will continue to generate demand for methods to assess the characteristics of thousands of new compounds using extremely small quantities. While not a

direct application of combinatorial chemistry, "labs-on-a-chip" have been developed to address the need for faster, more cost-efficient screening of thousands of compounds at once. "Several microfluidics companies and pharmaceutical firms are working on chip-based drug-screening systems capable of analyzing thousands of drug candidates at once.... For the most part, we are trying to take the conventional assays used in the drug industry and put them on a chip.... At present, however, these labs on a chip owe most of their appeal to their potential for doing the same job as existing equipment more quickly and at a much lower cost (Service, 1998)." Again, much of the current work is focused on drug discovery, yet the potential for spillover to other applications exists.

Toxicity is one class of characteristics that is of interest to new materials developers and environmentalists. In fact, combinatorial chemistry may be used to improve toxicity testing in the regulatory process by making it cheaper and more feasible to perform a variety of toxicity tests. Traditionally, potentially hazardous substances have been tested using rodent assays (Afshari et al., 1999). These assays require high doses, often take years to complete, and are expensive (Afshari et al., 1999). The information gained from rodents is then used to regulate chemicals to which humans are exposed (Afshari et al., 1999). Combinatorial chemistry has been used in conjunction with other technologies such as photolithography and solid-phase synthesis to create microfabricated DNA microarray chips that can be used to study gene function (Fodor, 1997). In 1999, National Institute of Environmental Health Sciences (NIEHS) researchers developed the ToxChip, a DNA microarray chip that allows scientists to analyze how human genes change in response to environmental agents (Medlin, 1999).

The ToxChip will not replace animal studies entirely, however it may reduce the use of animals in toxicological testing. In addition, it allows scientists to look more directly at the effects of toxic substances on human genes. Using the ToxChip, researchers can monitor the expression levels of thousands of different genes at a time, thereby condensing months of tedious and time-consuming research into a single day's work (Medlin, 1999). The human genes contained on the ToxChip were selected because they are involved in basic cellular processes and are proven to respond to different types of toxic injury (Medlin, 1999). Now that the more than 30,000 human genes have been identified (Venter et al., 2001), researchers can use this knowledge to identify the molecular targets of toxic substances. While the ToxChip is geared toward toxicological testing, similar DNA microarray technologies are being used for a variety of other applications, including drug development and cancer research.

While pure conjecture on our part, expanded use of combinatorial chemistry—as well as other rapid synthesis techniques that generate small quantities of large

numbers of compounds to be tested—could draw on microfluidics technological development, which would improve available testing procedures and equipment applicable for a range of human health and environmental concerns. The advantage of these techniques, as stated earlier, is that they are cheaper and faster to perform than traditional testing methods. Thus, more and improved data may become available for environmental decision making and risk analyses. The portable nature of these systems could also enable on-site testing should the situation warrant it. Moreover, toxicological testing and other health effects testing will likely be performed earlier in the development process over a wider range of potential candidate materials. This may lead to materials or catalysts that are optimized across a greater range of performance characteristics and dismissal of undesirable candidates earlier in the development process. As mentioned earlier, the OECD HPV testing program as well as the HPV Challenge Program and the endocrine disruptors activities are three current examples of where these capabilities would be useful.

Advanced Materials Discovery

Contrary to what one might initially think, the recent applications of combinatorial chemistry to a host of new materials and catalysts exploration could lead to significant benefits to the environment and human health. For just over five years researchers and companies have begun to apply these techniques specifically for new catalyst and new materials development. Initially employed for solid-state materials discovery, research papers describing the application of combinatorial chemistry to magnetoresistive materials, phosphors, dielectrics, ferroelectrics, polymers and polymer composites, semiconductors, catalysts and zeolites discovery have been published (Dagani, 1999). As these techniques mature, they could be used to find materials such as catalysts and materials in general that are preferred from an environmental point of view. A few examples and potential environmental benefits are described in the following paragraphs.

New catalyst discovery is challenging because catalysts are not well understood (Dagini, 1998; Smotkin, 1999). Combinatorial chemistry techniques are useful in this case because they generate large numbers of candidates for screening, which allows scientists to explore a greater range of compounds more readily without requiring specific knowledge of how these compounds may function. These techniques can also help scientists develop heuristics to improve their understanding of how catalysts function, which will inform future new catalyst discovery (catalysts that did not fit into existing heuristics have been discovered using combinatorial chemistry) (Smotkin, 1999; Kosla, 1999). As combinatorial chemistry is employed to facilitate the discovery of more efficient catalysts,

generally this would benefit the environment because improved manufacturing yields reduce energy use and waste generation. In addition, catalysts contain heavy metals so it is desirable to use lesser amounts of these materials. Heterogeneous catalysts, commonly used for remediating hydrocarbons and toxic wastes, are poorly characterized, require the use of solvents, and contain heavy metals. If these can be made more effective, then the costs and time required to remediate a large number of hazardous waste sites could be reduced. In addition, processes that use heterogeneous catalysts would use less heavy metals and solvents (Casebier, 1999; Smotkin, 1999).

The interviewees also suggested that combinatorial chemistry could give scientists the capability to develop new catalysts that meet a greater number of performance parameters. Traditional methods for catalyst development have focused on a limited set of parameters, those that characterize the reaction such as conversion efficiency and selectivity. Using combinatorial techniques, a larger set of parameters could include requirements for low toxicity by-products, more benign processing environments (such as low pressure, low temperature, or the use of aqueous solution versus using organic solvents), or other beneficial environmental features (Casebier, 1999). Comparing potential catalysts is easier using combinatorial chemistry because the new compounds are tested at the same time using the same methods and equipment (Dagini, 1998)—an advantage when optimizing across several parameters.

As an example, combinatorial chemistry has been used, at least in a preliminary sense, to search for better anode electrocatalysts for methanol fuel cell applications (Dagani, 1998; Reddington et al., 1998; Symyx, 1999b). One research team has found a catalyst that produces a current density 30 to 60 percent higher than a commercially available catalyst. While more testing has to be done before this catalyst is determined to be commercially viable, the research team believes this catalyst might not have been discovered at all using traditional methods because employing conventional methods to search for a catalyst comprised of four elements would have been time consuming and difficult to predict (existing catalysts for which this catalyst would replace are comprised of two elements) (Dagani, 1998). As fuel cell technology matures to the point where the team sees more widespread use, fuel cells could provide energy more efficiently over today's technology, lowering carbon dioxide (CO_2) and nitrous oxides (NO_x) emissions. Fuel cells that use renewable fuel sources, such as ethanol, for both stationary and mobile sources, are also desirable not only because of emissions reductions (CO_2, NO_x, ozone, etc.) but because future supplies of the fuel are not intrinsically limited (Smotkin, 1999; Weinberg, 1999).

Combinatorial chemistry techniques could also be employed to develop products with improved environmental features, such as reduced energy use or lower toxicity. These techniques are being employed to find higher-performing (structurally and magnetically) and cost-effective materials for permanent magnet applications. New materials such as permanent magnets will be required for transformers and electric vehicle applications. Improved thermoelectric materials, used for cooling and storage in microprocessors, portable power packs, electrical power generation from waste or geothermal heat, fuel cells, and many hot or cold storage containers, would benefit the environment through lower energy consumption and the use of alternative energy sources (Symyx, 1999b). Improved phosphors, used for fluorescent lights, computer screens, and flat panel displays, as well as new optoelectronic materials (e.g., light emitting diodes, LEDs) can improve the energy efficiency of these applications (Hewes et al., 1998). One available estimate stated that lighting consumes 25 percent of the electricity generated annually in the United States (Cawse, 1998). However, environmental gains will not likely be made without additional information and data on environmentally preferable attributes for new materials and catalysts, screening methods to identify compounds with these attributes, and testing methods that are employed during the discovery phase of new material development.

Finally, because combinatorial chemistry techniques use smaller amounts of materials in the discovery process, they reduce laboratory waste.

These environmental benefits discussed in previous paragraphs are not largely unique to combinatorial chemistry—other synthesis methods may provide the same benefits. However, clearly if combinatorial chemistry becomes more commonplace for new materials development, there are opportunities to introduce environmentally beneficial practices and results—often referred to as "green chemistry" by the EPA. As with many new approaches, the key to success will be in understanding what specific product features are better for the environment, educating and training science and engineering communities to develop products with these features, informing the public about these options, and ensuring that these products are compatible with markets. There is a strong governmental role for generating and disseminating information, creating niche markets and research funding.

In sum, combinatorial chemistry alone will not likely lead to an explosion in the numbers of new chemicals seeking regulatory review. These techniques may in fact make direct toxicity testing cheaper to perform, which would allow more testing to be done earlier in the process for potential candidates as well as for our legacy of chemicals in commerce. These techniques may also aid the

development of new environmentally preferable materials, reduce the environmental impact of producing goods, as well as speed the remediation of hydrocarbons. However, these gains will not likely be made without additional information and data on environmentally preferable attributes, large throughput screening methods to identify compounds with these attributes, and testing methods that are employed during the discovery phase of new material development. Applying combinatorial chemistry to new materials discovery is not well developed. The next section briefly identifies some of the technical hurdles that exist.

Challenges Remain

In general, combinatorial chemistry requires automation, miniaturization, and the ability to manage and interpret voluminous amounts of information. New software is required to assist in library design and to document the resulting compounds while automation and miniaturization of hardware is required for rapid synthesis at very small scales and analyzing micro amounts of compounds. Advances in these fields will facilitate the use of combinatorial chemistry.

While quickly approaching standard practice in the pharmaceuticals discovery process, the application of combinatorial chemistry to advanced materials science presents new challenges in the areas of high-throughput screening, synthesis, and information management. Methods for high-throughput screening large numbers of materials are not as straightforward nor are they as well developed as for organic compounds (Hewes, 1999; Smotkin, 1999; Weinberg, 1999). Organic compounds can be tested for biological activity with well-tested and common processes—such as "chemical means using gas chromatography, nuclear magnetic resonance spectrometry, mass spectroscopy, and incremental biological activity (Hewes et al., , 1998) ." While screening inorganic compounds on the other hand, techniques are needed to characterize the actual performance of the new material, and these can often be application dependent (Hewes et al., 1998). "Hundreds of different performance screens are used in new materials development and many of these screens are not designed, nor easily redesigned, for the small-volume samples generated by combinatorial chemistry (Dagani, 1999). For example, "Phosphor libraries are relatively easy to screen because devices that measure light intensity and color are either readily available or can be assembled from commercially available modules. Other properties, such as electrical properties, are much more challenging to measure in a quick, quantitative, and nondestructive manner (Dagani, 1999)." Not only will the screening techniques for inorganics differ, but in contrast to organics (where 80 percent purity is generally acceptable), the required purity levels of the material to be tested are higher in order to properly distinguish the performance characteristics (Hewes et al., 1998). And, for inorganic catalysts the morphology or roughly the structure and shape of the compound is much more critical to final performance (for example, fuel cells require catalysts with surface area-to-mass ratios in the range of 60 m^2/gm). Therefore, while combinatorial chemistry can help create interesting compounds to look at, it does not improve knowledge

regarding how the specific morphology affects catalyst function (Smotkin, 1999). Thus, one of the primary challenges for applying combinatorial chemistry techniques developed in the pharmaceutical industry to inorganic materials and catalyst discovery is the development of high-throughput screening techniques for a wide variety of properties.

Another issue for applying combinatorial chemistry to inorganics and materials development is the synthesis step itself. Most reactions used for the development of catalysts, phosphors, and polymers (and inorganic reactions in general) require higher temperatures and pressures than organic reactions used for drug development (Cawse, 1998). Furthermore, for a given sequence of reactions using the same set of reagents, inorganic reactions can require greater variations in the synthesis process in order to optimize the resulting compounds. And optimizing the synthesis process for each element of an array can be difficult (Smotkin, 1999).

Finally, since so many compounds are synthesized at once with combinatorial techniques, it is obviously preferable to work in smaller scales—at the microliter or microgram level. As candidate compounds move through the testing process through to production, larger and larger amounts of the compound need to be synthesized. While the pharmaceutical discovery process has developed techniques for scaling-up synthesis from microscopic samples, inorganic chemistry has not generally been performed at such small scales and therefore these scaling techniques have not been developed for the inorganics (Casebier, 1999; Hewes, 1999; Weinberg, 1999).

Bottom Line

Combinatorial chemistry techniques are enabling rapid and intelligent synthesis of new compounds—fundamentally increasing our ability to create new chemical compounds and materials with desired qualities. If this is recognized early, combinatorial chemistry—as well as other new synthesis methods—could be harnessed to develop environmentally preferred products and processes. For example, improved catalysts, more efficient energy conversion, better thermoelectric materials, and so forth can reduce toxic substances use, reduce pollution generation, and improve energy efficiency. As with many new approaches, the key to success will be in understanding what specific product features are better for the environment, educating and training science and engineering communities to develop products with these features, informing the public about these options, and ensuring that these products are compatible with markets. There is a strong governmental role for generating and disseminating information, creating niche markets and research funding.

While the potential exists, most experts do not anticipate overrunning the regulatory process with a large stream of new chemicals discovered through the use of combinatorial techniques. In fact, an enhanced understanding of how chemicals affect gene function and laboratories-on-a-chip technology (whose demand is driven by new synthesis methods and in some cases the labs are actually produced using combinatorial techniques), may make direct toxicity testing of new compounds assessed in the regulatory process cheaper and quicker to perform. As a result, there may be an enhanced ability to perform direct toxicity testing for both new and existing chemicals. More toxicity data could also help the application of structure activity relationship analysis for extrapolating health and environmental impacts to like compounds when direct testing is not practical. Regarding testing of new chemicals, should these techniques lend themselves to improved toxicity testing and testing for a greater variety of issues, the government role is essential. Strong institutions are important mechanisms for balancing risks and benefits—across a multitude of stakeholders—associated with new technologies. To ensure public confidence in the process, institutions that can assess the science, collect data, communicate findings, and balance competing interests in an open setting are essential. This will be important if toxicity test data from labs-on-a-chip are to be accepted.

A. Combinatorial Chemistry as Part of a Larger Tool Set to Find New Compounds

Because combinatorial chemistry can be thought of as a methodology, or series of techniques, it supports many other areas such as molecular modeling, biocatalysis, and directed molecular evolution. Other developing synthesis methods could be used to produce environmentally preferable products or to improve manufacturing processes. Some of these techniques can be used with combinatorial chemistry; others are separate but rely on the same advancements in information and automation technologies.

For example, combinatorial techniques are used in concert with molecular modeling to find compounds with specific desired properties. Molecular modeling on its own has already been used to look for catalysts for creating polyethylene foam without Freon, a solvent for new plastics recycling, and CFC substitutes (Parkinson and Fouhy, 1996). Because molecular structures and structure-property relationships are not well understood, molecular models cannot always be constructed. As a result, some are using combinatorial chemistry to refine the heuristics of what makes a better new material because it is difficult to completely understand how and why certain molecular structures perform the way they do.

Combinatorial chemistry is also one of many tools that may advance our knowledge of how chemicals affect gene function. Libraries generated through combinatorial chemistry are currently mined not solely to discover a better product for a given application. Scientists are using libraries generated by combinatorial chemistry to learn more about how genes work—by analyzing the impacts of gene perturbations. Expanded knowledge on gene function could be used to develop products with desired features, for example, combinatorial chemistry could help identify the specific gene action that could be modified to make herbicides that degrade more rapidly in the environment (other factors also influence biodegradation). Combinatorial chemistry could also be one of the technologies used to refine candidates from natural products into marketable products (Kosla, 1999). Knowledge regarding the interactions of chemicals, genes, and cell function can also improve toxicity studies and chemical risk analyses used in environmental decision making and regulatory processes.

In another technique, combinatorial biocatalysis is used to speed the natural process whereby modified enzymes produce new organic biomolecules, enhancing the diversity of natural systems. Combinatorial biocatalysis uses natural catalysts (such as natural, recombinant, and engineered enzymes) in various combinations to create organic libraries suitable for pharmaceutical and agrichemical candidates. Because of conditions in nature, these reactions are, in general, highly efficient, have high yields, generate few by-products, are highly selective, and occur in low-temperature, low-pressure environments (Michels et al., 1998). Natural enzymes used as catalysts in industrial processes with these features would have obvious environmental and human health benefits. To the extent that these techniques can enhance the development of new agrichemicals, there could be benefits to the environment and human health if they have lower toxicity, more rapid degradation, and other desirable features. Combinatorial biosynthesis on the other hand seeks to alter organisms to produce the desired product directly. It can be used to produce libraries of organic compounds built from natural and non-natural building blocks (Verdine, 1996). Expanded use of combinatorial biosynthesis could generate additional support for sustaining biodiversity as nature is explored for new compound possibilities.

One final related synthesis method in the continuum is directed molecular evolution. First employed in the late-1980s, directed molecular evolution is the biotechnology analog to rapid chemical synthesis and combinatorial chemistry. Directed molecular evolution seeks to speed the natural process of gene evolution by actively creating genetic diversity and searching for the resultant genes that have preferred traits. Diversity is created by combining genes or by artificially inducing mutations (using radiation, chemicals, etc.) to create thousands of new gene combinations. These genes are screened in any number of ways for the traits desired. Hopefully these genes will carry instructions for novel proteins or enzymes that will generate desired qualities that are improved by orders of magnitude. And then the process can be repeated to continue to improve the trait of interest or to add a new trait.

In the late-1990s Novo Nordisk isolated a natural enzyme using directed molecular evolution for use in stain remover (Jacobs, 1999). Biologically based enzymes, the protein that acts as a catalyst between molecules in a cell, as catalysts are less toxic, cleaner, operate in milder conditions (temperature and pressures), are more efficient, and promote more specific reactions than synthetic catalysts. Natural enzymes could be used as catalysts to replace the synthetic catalysts typically used in manufacturing today, also replacing coal and oil sources of carbon with plant-based renewable sources. DuPont, for instance, has developed a process to manufacture polyester intermediates using glucose from

cornstarch (a renewable) and enzymes from a microorganism (in this specific case the enzymes were developed using recombinant DNA and not directed molecular evolution). This process does not require heavy metals, petroleum, or toxic chemicals and the liquid effluent is biodegradable and the microbial by-product can by used as animal feed. DuPont has a patented process to unzip these molecules for recycle (Krol, 1997; Halliday, 1998). Directed molecular evolution is also being used to increase food production by making crops or livestock more productive. And it could be used to find useful microbes to remediate harmful by-products of industrial processes. However, directed molecular evolution, and biotechnology in general may have its downside with respect to the environment as well. For example, genetically improved crops could have unintended side effects such as quickening the pace of development of resistant strains of insects or weeds, killing non-targeted species of plants, insects and animals, or causing allergic reactions in some consumers. These are just a few examples of how biotechnology, through directed molecular evolution, could affect the environment—by less energy use, lowered use of toxins in industry, greater use of renewable resources as opposed to nonrenewable oil greater food production, and generation of resistant weeds or insects—but there are many others.

The extensive international debate surrounding the efficacy of regulatory processes on these matters illustrates the difficulties in managing the risks and benefits associated with new technologies. Advancement in new synthesis methods can potentially put additional pressure on regulatory processes and risk-assessment techniques.

BOX 2: Environmental Impacts of Combinatorial Chemistry and Other Synthesis Methods

Catalysts

Nontoxic, noncorrosive biocatalysts for less harmful chemical production.
Biocatalysts that may be reused or recycled.
Biocatalysts that may degrade rapidly in the environment.
Catalysts that do not generate undesired by-products, have high yield, and are efficient.
Catalysts for soil remediation of dechlorinated hydrocarbons.
More efficient and smaller electrocatalysts in a methanol fuel cell.

New Materials

Phosphors that provide light with less energy consumption.
Thermoelectric materials for cooling and storage that are more efficient.
Permanent magnets with better performance and cost-effectiveness for electric vehicles and transformers.

Drugs

Improved ability to mimic natural compounds.

Other

Understanding gene influence on cell function.
Natural products may put additional pressure on mining and preserving biodiversity.
Improved understanding of chemicals' influence on genes and cell function for use in environmental risk analyses and regulatory decision making.
Unintended side effects of genetically engineered crops—allergic reactions, effects on non-target species.

B. Combinatorial Chemistry Timeline

A Brief History of Combinatorial Chemistry and Directed Molecular Evolution		
early 1960s	First demonstration of directed molecular evolution. Sol Speigelman of the University of Illinois artificially bred RNA molecules to have a rapid replication rate. The resultant molecule was 83% different from the original ancestor molecule and could replicate itself 15 times faster.	"Without Miracles: The Artificial Selection of Organisms and Molecules," post-1994.
1963	Introduction of solid-phase peptide synthesis by Merrifield, providing the initial basis for combinatorial chemistry.	VanDrie, 1998.
mid 1980s	Methods for attaching an array of distinct peptides to a chip are developed by Affymax.	VanDrie, 1998.
late 1980s	Two techniques are developed that pave the way for greater use of combinatorial techniques. H. Mario Geysen develops a technique to synthesize arrays of peptides on pin-shaped solid supports. Houghten develops a technique for creating peptide libraries in tine mesh using solid-phase parallel synthesis.	Borman, 1998.
late 1980s/ early 1990s	Combinatorial Chemistry first employed for drug discovery.	Thayer, 1996.
c. 1989	Directed molecular evolution began.	Chui, 1999.
1991	"Split-and-mix" approach to synthesize large numbers of peptides developed by Houghton et al. (Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H., "Generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery," *Nature*, Vol. 354, 1991, pp. 84–86.)	VanDrie, 1998.

1991	Application of combinatorial chemistry to analysis of genetic information with the founding of Affymetrix.	http://www.Symyx.com, accessed July 1999.
1992	Seminal report bon combinatorial chemistry describing the rapid synthesis of a large library of benzodiazepines by Bunin and Ellman (Bunin, B. A.; Ellman, J. A., "A general and expedient method for the solid-phase synthesis of 1,4-benzodiazepine derivatives," *J. Am. Chem. Soc.* 1992, *114*, 10997-10998.)	VanDrie, 1998.
	First drugs discovered using combinatorial chemistry:	
1992	Thomas Webb at Corvas International discovered an orally active thrombin inhibitor, which entered clinical trials.	Borman, 1998.
1994–1995	Eli Lilly identified an orally active central nervous system agent, which entered clinical trials in November 1995 by using combinatorial chemistry to optimize an existing lead. This is one of the first small-molecule combinatorial chemistry compounds to be given to humans.	Borman, 1996.
1994	Gene shuffling for directed molecular evolution developed by Stemmer.	Chui, 1999.
1995 (1995–1998)	First application of combinatorial chemistry to inorganic compounds. Schultz and Xiang demonstrated the use of combinatorial chemistry for solid-state materials discovery.	Dagani, 1999, Weinberg, 1999, and Casebier, 1999.
1998	Novo Nordisk began marketing a variant of a natural enzyme (used to remove stains from clothing) that was originally isolated from a fungus and modified through directed molecular evolution.	Jacobs, 1999.

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